PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/003183	23.07.2004	25.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/5517, A61P35/00, C07D487/06

Applicant
CANCER RESEARCH TECHNOLOGY LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/003183

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 30-32

because:

☒ the said international application, or the said claims Nos. 30-32 with respect to IA relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/003183

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3,5-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations

see separate sheet

10/565308
International application No.
PCT/GB2004/003183

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

Re Item III.

1 Claims 30-32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item V.

1 The following documents are referred to in this communication:

D1 : WO 01/16136 A (CANCER RES CAMPAIGN TECH ; AGOURON PHARMA (US)) 8 March 2001 (2001-03-08)

D2 : WO 00/42040 A (CANCER RES CAMPAIGN TECH ; CANAN KOCH STACIE S (US); WEBBER STEPHEN EV) 20 July 2000 (2000-07-20)

D3 : CANAN KOCH S S ET AL: "Novel Tricyclic Poly(ADP-ribose) Polymerase-1 Inhibitors with Potent Anticancer Chemopotentiating Activity: Design, Synthesis, and X-ray Cocrystal Structure" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 45, 2002, pages 4961-4974, XP002304613 ISSN: 0022-2623

2 The invention relates basically to four independent compounds I, II, III and the phosphate of I according to claims 1-4, with each compound having first and second medical use claims and claims drawn to pharmaceutical compositions comprising the said compounds. Further claims 30-32 relate to methods of the treatment of the human or animal body.

2.1 The compound I is already known from example IIII disclosed on pages 97-98 of D2. This compound is said to be a PARP inhibitor, hence, the disclosure of D2 is also considered to take away the novelty of claims 5,8,11-14,17,20-21,24-25, 28-30. These claims do no meet the requirements of Art. 33(2) PCT.

The phosphate salt of compound I is not specifically disclosed in any of the cited documents. Hence, the subject-matter of claim 4 appears to be novel in the sense of Art. 33(2) PCT.

The compounds II and III are already disclosed in D1, examples 141 and 58. Since the compounds of D1 are PARP inhibitors, the subject-matter of present claims 6-7,9-13,15-16,18-20,22-24,26-29, 31-32 is not new in the sense of Art. 33(2) PCT.

2.2 The present application does not meet the criteria of Art. 33(1) PCT, because the claimed subject matter does not involve an inventive step in the sense of Art. 33(3) PCT.

All of the cited documents relate to the activity of the presently claimed compounds, namely the ability to inhibit PARP. The compounds are therefore useful to treat various forms of cancer. Given the fact that all, but the present phosphate salt of compound I, are already known for this medical utility from the prior art, and taken into consideration, that phosphate salts of the present compound type are explicitly taught by D1 (page 14, line 18) and D2 (page 13, line 19), the skilled person would have expected that the present compounds in salt form are likewise useful to treat cancer. The skilled person would also base his expectation on the established structure-activity for tricyclic compounds, which bear amino groups in para position of the 2-aryl moiety (see D3). From page 4966 of D3, the skilled person was aware that the "PARP-1 binding site appears to be fairly tolerant of a variety of functional groups at each phenyl regioisomer". He was also aware of the beneficial solubilizing effect arising from the introduction of amine groups at the said para position of the phenyl ring (see D3, page 4966, left column). Hence, the provision of the present PARP inhibitors is considered to be an obvious solution to the problem of providing further anticancer agents. Since pharmaceutically acceptable salts thereof are likewise taught, of which the phosphate salt is specifically disclosed in D1 and D2, it is not apparent in how far the phosphate salt should have properties other than the beneficial solubility and medical utility already described in detail for the compounds I, II and III. The requirements of Art. 33(3) PCT are therefore not considered to be met by the present claims.